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(6) PREVENTION OF INFLUENZA AND OTHER RESPIRATORY DISEASES. (U)

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BY

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CONTENTS

I. Observations on Antibody Levels of 1977 Influenza Patients

A. Introduction

The availability of paired sera from groups of nonvaccinated and vaccinated persons with influenza made it possible to follow up earlier observations on the relationships between serum antibody of different types and susceptibility to clinical influenza. It is now generally accepted that influenza cases occur mainly in persons with low or unmeasurable HI antibody titers and that, as the titer increases cases become increasingly rare. This relationship holds only if the strains used in the test are identical to those causing the epidemic and if non-specific inhibitors are removed by appropriate treatment of the sera. In this laboratory a titer of 16 has repeatedly been shown to represent the point beyond which very few cases occur. The Center for Disease Control has chosen 40 as the "protective level" and assesses the potential protective effect of vaccine on the proportion of vaccinated persons who reach or achieve that level.

Occasionally, however, influenza occurs in persons with high HI antibody titers. Perhaps there are persons who fail to produce sufficient antibody at the site of invasion, either from local production or from serum sources. On the other hand, it is possible that in these instances the HI antibody does not accurately reflect neutralizing antibody. It has been shown that neuraminidase antibody may contribute to the hemagglutination-inhibiting antibody response. In order to learn more about this perplexing problem the sera from influenza patients in this epidemic were studied in detail.

The patients on whose sera the studies were run were ill during the outbreak at Lowry Air Force Base in February and early March of 1977. The influenza strain responsible is identified as A/Denver/1/77. It was brought to Lowry AFB by incoming students from Lackland AFB and resembles the A/Texas/77 strains. The vaccines used were whole virus preparations of influenza A containing 400 CCA units of A/New Jersey/76 and 400 CCA units of A/Victoria/75. The influenza B component was a split virus vaccine containing 500 CCA units of B/Hong Kong/72. Vaccine was given soon after personnel entered the Air Force at Lackland during the months of October, November or early December, following which vaccination was stopped. The interval between vaccination and illness was in most instances 2 to 4 months. Twenty-three cases of influenza A in unvaccinated students and 30 in vaccinated students were detected during the outbreak early in 1977.

B. HI antibody levels for 5 H3N2 strains in sera of persons who had clinical influenza

1. Hemagglutinating-inhibiting antibody

a) Unvaccinated persons

Each of the 23 patients had antibody for A/Hong Kong/68,

the earliest H3N2 virus (Table 1). Increasing numbers were seronegative in tests with later members of the H3N2 family. Five were seronegative in tests with A/England/42, 10 with A/Port Chalmers/73, 16 with A/Victoria/75 and 20 with A/Denver/77. A small number of persons had titers for A/England/72 which were equal to or higher than those for A/Hong Kong/68, suggesting that their initial contact with the H3N2 virus occurred in 1972 or 1973 rather than in the period between 1968 and 1972. There were 5 such persons in the group of 23. Titers were lowest for A/Denver/77. The data indicate that all had been infected by an influenza A virus of the H3N2 family early in the 1968-77 period. They had lost enough of their immunity during the following years so that they were susceptible to clinical infections when exposed to the A/Denver/77 strain.

These observations are of interest in that they shed some light on the cycling of influenza virus families. It has long been believed that each family disappears when the level of immunity rises to a point where spread from one susceptible person to another becomes very unlikely or impossible. Highest attack rates occur during the period immediately after a new strain appears and subsequent outbreaks tend to be smaller as increasing proportions of the populations become resistant. This is an acceptable generalization, but there may be segments of the population which have escaped the initial wave and these may experience epidemics with high attack rates.

b) Vaccinated persons

In vaccinated persons who had clinical influenza the pattern of antibody distribution was similar, but was set at a higher level (Table 2). The highest titers were observed in tests with A/Hong Kong/68. While there were 2 persons with titers of less than 8, most had titers of 64 or more and 9 of 30 had titers of 1024 or higher. The A/Victoria/75 vaccine thus appeared to have boosted sharply the antibody levels to the older strains, A/Hong Kong/68, A/England/72 and A/Port Chalmers/73, the strains which had been the cause of earlier illnesses in these persons. On the other hand, only one half had antibody for A/Victoria/75 and for A/Denver/77 and the other half had relatively low titers. Three persons had titers of 128 or greater for A/Victoria/75 and 1 had a titer of 1024 for A/Denver/77.

Several explanations were sought for the fact that a few persons had clinical influenza despite their high HI antibody titers. These included (1) the presence of serum inhibitors (2) misdating of the onset of illness, with the "acute" serum actually being collected so late that antibody titers had already risen and (3) high levels of neuraminidase antibody which might have participated in the observed hemagglutination inhibition. With respect to inhibitors,

sera were treated with RDE, periodate and trypsin, but titers were unchanged. The dating of the onset of illness was taken from the record of the project secretary and must be assumed to be accurate. The possible role of neuraminidase antibody will be discussed in a later section.

C. Complement-fixing antibody (Table 3)

1. Unvaccinated

Twenty of 23 patients with influenza had titers of less than 8 and the remaining 3 had titers of 8 or 16. All had titers of 16 or higher in the convalescent sera with most between 32 and 128. Twenty-two of the 23 had 4-fold or greater increases in titer.

2. Vaccinated

Twenty-one of 30 had titers of less than 8 in their acute phase sera. The remaining 9 had titers between 8 and 32. In the convalescent sera 28 of 30 had titers between 32 and 256. Twenty-eight of the 30 persons showed a 4-fold or greater increase in titer.

The fact that very few of the unvaccinated persons had measurable antibody parallels the observations of earlier studies: complement-fixing antibody after initial infection is usually relatively short lived. It has been noted above that all the individuals in these groups showed, by the presence of HI antibody, evidence of infections many years earlier in the H3N2 decade, usually between 1968 and 1972.

The distribution of titers in the acute sera of vaccinated persons was only moderately higher than in the unvaccinated. The titers of persons bled 3 weeks after receiving vaccine of the potency used in this study have usually been considerably higher, but have tended to decline rapidly. Convalescent titers were only marginally higher than in unvaccinated persons.

D. Neuraminidase inhibiting antibody (Table 4)

1. Unvaccinated

The acute phase sera of 17 of 23 unvaccinated persons with influenza failed to show inhibition of neuraminidase of the X-48 strain (HEq1N2). The remaining 6 had titers of 8 or 16. The convalescent sera showed a sharp upward shift, with only 2 sera remaining at the less than 4 level. Only 3 of the 23 serum pairs failed to show a 4-fold or greater increase in titer.

2. Vaccinated

All but 4 of 30 acute phase sera had NI antibody. The titers

were relatively low in most instances. A number of the convalescent sera had markedly elevated titers (≥128), but 5 persons had titers of 8 or less. Ten of the 30 persons failed to show a 4-fold or greater increase in titer.

3. Comment

This laboratory has had far less experience with the NI test than with the HI test, and the NI test is far more difficult to standardize. During the past year the test appears to have performed well and results have been reproducible within narrow limits.

It is generally believed that the clinical manifestations of influenza will be aborted or at least modified in persons who have neuraminidase inhibiting antibody. The data presented here indicate that this may be a relative rather than an absolute relationship. The severity of illness in persons with antibody, as shown by the height of their temperatures, did not appear to differ from that of persons without antibody (Table 5).

E. Serologic diagnosis of influenza

A comparison of the effectiveness of different serologic tests in detecting a diagnostic (≥4 fold) rise in titer in unvaccinated persons is presented in Table 6. In complement-fixation tests using as antigen allantoic fluid from chick embryos infected with A/Victoria/75 96% had 4-fold rises. In HI tests with the earlier strains 4-fold titer increases were found in less than two-thirds of the paired sera tested. Results were better with A/Victoria/75 and best with A/Denver/77, with which 4-fold rises were found in 96%. The distribution of titers is shown in Table 7. In neuraminidase inhibition tests, as in the complement-fixation tests, most persons lacked antibody in their acute phase sera, but only 87% showed 4-fold increases in titer.

In vaccinated patients (Tables 8 and 9) antibody was more frequently found in the acute sera and increases in titer of 4-fold or more were less often demonstrated. The complement-fixation continued to be highly effective for diagnosis (87%) and the best results continued to be obtained with the HI test using the strain A/Denver/77 isolated from the outbreak (93%). However, earlier strains including A/Victoria/75 showed diminishing usefulness (70%). The neuraminidase inhibition tests with X-48 antigen demonstrated significant increases in titer in only 65% of patients.

It appears, therefore, that either the complement fixation test or the HI test using an homologous strain isolated from the epidemic are highly sensitive diagnostic methods. A cautionary note should be made that some freshly isolated strains may be relatively or markedly non-avid during early passages. The earlier H3N2 strains become less useful in HI test as the distance from the current strain increases. The NI test was not as useful as the HI test with A/Denver/77.

These observations are important because they emphasize the value of serologic testing during current outbreaks. From 1972 to 1975 virus strains were very easily isolated and isolation rates exceeded 90%. During that period a reasonably accurate estimate of decreased incidence could be made on the basis of virus recovery alone. However, in 1977 these figures fell to slightly more than 60%. If no serologic testing had been done a falsely low incidence of influenza would have been reported.

II. Further Studies on Neuraminidase Antibody

The neuraminidase antibody response to military formula vaccine (400 CCA units of A/New Jersey/76 and 400 CCA units of A/Victoria/75) sera from 49 patients who were ill before influenza appeared on the base was tested using strain X-48. These sera were collected from persons who had received vaccine 2 or 3 months earlier at Lackland AFB.

Because of the laborious nature and cost of this test sera were run at one dilution only, namely 1 to 16. Fifty-seven percent of the sera had titers of 16 or higher and 43% had titers of 8 or less. This distribution is different from that observed in vaccinated persons who became ill with influenza. In the latter group 40% had titers of 16 or more and 60% had titers of 8 or less.

Estimates were made, on the basis of extrapolations, of the attack rates in vaccinated persons with NI titers of 8 or less and in those with titers of 16 or more. The clinical illness rate was 1.12% in the former and 0.56% in the latter (2:1). When the same method of calculation was applied to attack rates at different HI antibody levels observed, the illness rate was 4.1% in persons with titers of 8 or less and 0.5% in those with titers of 16 or higher (8:1). It appeared that, in vaccinated persons, the NI antibody titer was less predictive of protection against illness than the HI antibody level.

These data are in conflict with generally held concepts and are admittedly based on very small numbers. Our data on unvaccinated patients show that clinical influenza is infrequent in persons who have elevated NI antibody titers. Unfortunately we are unable to estimate attack rates in this group because all had been vaccinated before arriving at Lowry.

III. PR8 Antibody in Recipients of A/New Jersey/76 Vaccine

It was noted in last year's report that persons who received A/New Jersey/76 vaccine, particularly whole virus vaccines, developed PR8 antibody with unexpected frequency. A limited PR8 response was anticipated because of known antigenic relationships between Hsw and H0 strains, but the PR8 response was expected to be less than that to A/New Jersey/76. This was not the case. Many persons, including persons under 19 years of age showed no A/New Jersey/76 response but developed high titers of HI antibody for PR8 antigen.

Many sera which demonstrated this pattern repeatedly in earlier tests with four different PR8 antigens now no longer react with three lines of the PR8 strain which originated from Ann Arbor. However, they still react as before with Dr. Marine's PR8 antigen.

Twenty pairs of serum were sent to Dr. Kilbourne in order to compare results obtained here with those in his laboratory. We also forwarded a vial of the Marine antigen. The sera represented (1) persons under 19 who had shown PR8 titer rises without any A/New Jersey/76 rise, (2) persons in their early twenties with the same pattern and (3) older persons who had PR8 antibody in their prevaccination sera, presumably representing bona fide PR8 antibody as a result of priming early in their lives.

Eleven of these serum pairs have been tested in Dr. Kilbourne's laboratory (Table 10) and results are remarkably discrepant. With "PR8 antigen" rises were observed with the same serum pairs in both laboratories, but the titers were much lower in Dr. Kilbourne's laboratory. In the Denver laboratory the results obtained with "PR8" and Marine antigens were similar, except with sera 1, 3, and 5, where the antibody noted in earlier tests with "PR8" antigen had disappeared. The most obvious differences were seen when the results obtained with Marine antigen are compared. None of the last six sera (8, 9, 10, 13, 15, 19) which were selected because they contained PR8 antibody, showed any titer in their prevaccination sera in Dr. Kilbourne's laboratory. As noted in the table this may have been due in large measure to the fact that the antigen was used there in far higher concentration than we have found appropriate in many tests in our laboratory.

The situation, therefore, remains confused. Additional Marine antigen is being sent to Dr. Kilbourne's laboratory at his request so that he may repeat the tests with all 50 of the paired sera which he received.

IV. Influenza in the Denver Area - November 1977 through January 1978

Influenza A was first detected in the fall of 1977 in an unvaccinated member of the permanent party who was stationed at Buckley Field and resided in Aurora, an eastern suburb of Denver. The date of onset was 2 November. A second case, also in a member of the permanent party occurred during the following week. Both were shown to have been caused by A/Victoria/75-like strains. Vaccine was given basewide between 6 November and 12 November. Two additional cases of influenza A of the A/Texas/77 type occurred on 18 and 30 November, but none were observed in December. In January there were 3 cases, one of A/Victoria/75 and two of A/Texas/77 type. Four of the seven persons had not received vaccine.

During this period influenza A of both the A/Victoria/75 and A/Texas/77 types was occurring at a low incidence throughout the Denver area. During December and January 70 strains were isolated. Initially all were of A/Victoria/75 type, but later a few (3) were of A/Texas/77 type. Three strains gave identical titers with A/Victoria/75 and A/Texas/755 antisera. Several came from patients in the University Hospitals who were severely or even fatally ill.

A remarkable and tragic outbreak occurred in a nursing home in Brighton some 15 miles northeast of Denver. There 42 of approximately 100 residents, all elderly became ill with typical influenzal illness during the week of 18 December and 7 died. Influenza A virus was isolated from 3 of 4 throat washings collected from acutely ill patients but not from the lungs of 2 patients who died several days after onset. The strains were of the A/Victoria/75 type. Many of the patients had received influenza vaccine the year before.

The fact that influenza A failed to produce more than a scattering of cases in the face of its continuing occurrence in the surrounding community is of considerable interest and importance. The virus was introduced into the base population on at least 7 occasions but failed to spread. This situation has been observed several times in the past during outbreaks of influenza A in the community and during an influenza B outbreak last year. It is probably best explained by the fact that vaccination had raised the antibody levels of the base population to a point where there were too few susceptibles to support virus spread. The HI antibody titers of vaccinated persons who were seen during this period with other illnesses supports this interpretation. HI antibody titers of 16 or greater were found in 96% of persons in tests with A/Victoria/75, 86% with A/Texas/77 and 92% with B/Hong Kong/72 (Table 11).

V. Studies on Antibody Levels for New H1N1 Strain (A/USSR/90/77)

A. H1N1 antibody response to A/New Jersey/76 vaccine

Following the receipt of information that a new influenza A strain in the H1N1 family had swept across the USSR and had appeared in Hong Kong a number of tests were run to determine the HI antibody levels for H1N1 virus strains in sera of persons in different age groups and in recipients of A/New Jersey/76 vaccine. The latter was done on the chance that there might be sufficient cross between A/New Jersey/76 and the new strain so that one or two injections of A/New Jersey/76 vaccine might evoke sufficient antibody response to provide some protection. Results of these studies were summarized in a letter forwarded to Colonel Franklin Top at Walter Reed Army Institute of Research (WRAIR) on 3 January 1978 and are incorporated in this report with only minimal changes.

In the course of investigating the PR8 antibody response to A/New Jersey/76 vaccines sera from 20 persons who had shown no antibody response to A/New Jersey/76 but had shown moderate increases in PR8 antibody titer were tested against H1N1 strains. Rather surprisingly, the majority showed increases in titer to FM1. The post-vaccination titers were relatively low, most often 16 or 32. In tests with A/AA/56, a late H1N1 strain, only 2 of 20 serum pairs showed any increase in titer.

With the appearance of an H1N1 epidemic in the USSR and in Hong Kong these observations were extended. Sera from 3 groups of individuals who had received vaccine in 1976 were studied. The first consisted of Air Force personnel, age 17 to 19, who initially received one of the test lots of A/New Jersey/76 vaccine in the spring of 1976 and 6 months later received bivalent whole virus vaccine containing 400 CCA units each of A/New Jersey/76 and of A/Victoria/75. These persons had been born after the H1N1 virus had disappeared. The second group consisted of medical students, age 23 to 32, who presumably had their initial exposure to H1N1 strains in the decade from 1947-57. The third group was made up of laboratory personnel at the Blood Bank and ranged in age from 33 to 61. Most had been born during the HON1 era and had presumably had their initial exposure to HON1 strains. Both the latter groups received bivalent vaccines, either whole or split, containing 200 CCA units of A/New Jersey/76 and of A/Victoria/75. Studies on a group

of medical students in the same age range as group 2, who had received an H3N2 vaccine a year earlier, showed no FM1 antibody response, indicating that the results described below were attributable to the A/New Jersey/76 component of the bivalent vaccine.

The serum pairs tested against the early FM1/47 and a late A/AA/57 strain in order to observe the effect of the antigen drift which occurred during the H1N1 decade. The aberrant A/Denver/57 strain, which appeared in the last year of the H1N1 period, was not tested because it was so different from other members of the H1N1 family.

The results obtained with the FM1 strain are shown in Table 12. In group 1, age 17 to 19, none of the 25 persons had titers of 16 or more in their prevaccination sera. Four of 25 showed 4-fold rises in titer after the first injection of vaccine and 15 of 25 after their second injection. Group 2, age 23 to 32, behaved very differently. Twenty-two of 38 had titers of 16 or more in their prevaccination sera and an additional 5 had titers of 8. Following vaccination 63% had a 4-fold increase in titer and 87% had titers of 16 or higher. In group 3, age 33 or more, 9 of 15 had titers of 16 or more in their prevaccination sera. However only 3 of 15 (20%) showed a 4-fold increase in titer and 67% had post-vaccination titers of 16 or higher.

The results with A/AA/57 strain are shown in Table 13. The general pattern was similar but the antibody response was uniformly lower. Thus in groups 1 and 3 no persons had post-vaccination titers higher than 32 and the proportion of persons with post-vaccination titers of 16 or higher was only 33% in group 3 and 24% in group 1. Only in group 2, the group primed with H1N1 viruses, did the response approach that observed with A/FM1.

With the strain A/USSR/90/77 results were very similar to those observed with A/AA/57 and quite different from those with A/FM1/47 (Table 14). In persons under 20 years of age the response was negligible even after 2 injections of vaccine. In the 23 to 32 year age group the majority showed a 4-fold increase in titer and 74% had post-vaccination titers of $\geq$16. Few persons over 33 had elevated antibody titers and few showed significant increases in titer.

Finally, the current HI antibody levels for A/USSR/90/77 in patients seen in the Lowry Clinic for febrile upper respiratory infections is shown in Table 15.

Summary and Conclusions

1) A/New Jersey/76 produced an antibody response to FM1 which might produce relatively good protection against H1N1 challenge in the age group 23 to 32 if the new strain was antigenically closely related to FM1.

2) A single injection of A/New Jersey/76 vaccine in younger or older persons provided an antibody response inadequate for protection.

3) A double injection of vaccine in younger persons raised the level of antibody to "protective" levels for the FM1 strain in 64% of persons but for the A/AA/57 strain to only 33%.

4) The difference in response to the FM1 and A/AA/57 strains points out clearly the risk of basing any predictions on tests with the FM1 strain alone.

5) While the response observed in tests with A/USSR/90/77 clearly shows the relationship between FM1 and this new H1N1 virus, the antigenic difference is sufficiently great that A/New Jersey/76 vaccine offers virtually no promise for protection during an A/USSR/90/77 epidemic.

B. A/USSR/90/77 HI antibody response to FM1 vaccine

In 1971, Dr. William Marine, Chairman of the Department of Preventive Medicine at the University of Colorado, studied the response of a large number of persons of different ages to monovalent A/FM1/47 vaccine. The vaccine was a whole virus preparation made by Merrell National and contained 571 CCA units. Sera from these patients had been stored in a frozen state and were kindly made available by Dr. Marine for testing against strain A/USSR/90/77.

In interpreting the results it should be noted that persons listed as <17 would now be <23 and those listed as >18 would now be >24. The response to the homologous FM1 strain was remarkably good, even in persons less than 17 years of age (Table 16). On the other hand the response to the A/USSR/90/77 was relatively poor (Table 17). In the under 17 group only 39% had titers following vaccination of $\geq$16 and in the "primed" over 18 group the comparable figure was only 84%.

These data again point out the considerable antigenic different between A/FM1/47 and A/USSR/90/77, and suggest that an A/FM1/47 vaccine would protect poorly in an A/USSR/90/77 epidemic. There is a suggestion in this test and in those reported above that the A/USSR/90/77 strain may be somewhat non-avid. The differences observed might be less if the tests were repeated with a better adapted strain.

VI. Summary

1) Antibody studies on 23 unvaccinated and 30 vaccinated persons with A/Texas/77 influenza showed that almost all had been infected previously with H3N2 strains. HI titers were highest against the earliest strain and diminished progressively with more recent strains. They were lowest with A/Denver/77, the epidemic strain.

2) Neuraminidase inhibiting (NI) antibody titers were low in the acute sera of unvaccinated persons, but 15 of 33 vaccinated persons had titers of $\geq$16. The NI titer levels were of less value in predicting protection against influenzal illness than HI antibody levels against the epidemic strain.

3) The most useful tests for serodiagnosis were HI tests using the epidemic strain and complement-fixation tests. NI tests and HI tests with earlier H3N2 strains were less sensitive, particularly in vaccinated persons.

4) The Lowry Air Force Base population, which had received A/Victoria/75 vaccine in November, 1977 had only a scattering of cases of influenza even though influenza A, mainly A/Victoria/75, was widespread in the Denver area in December, 1977 and January, 1978.

5) HI tests for antibody for H1N1 strains showed that persons under 23 years of age lacked antibody for A/FM1/47, A/AA/57 or the new epidemic strain A/USSR/90/77. A large proportion of persons between 23 and 32 and a smaller proportion of older persons had antibody. Titers were considerably higher for A/FM1/47 than for A/AA/57 or A/USSR/90/77.

6) Persons between 23 and 32 who had received A/New Jersey/76 vaccine showed increases in titer to all 3 H1N1 strains. Persons younger or older than this showed almost no response in tests with A/USSR/90/77.

7) A monovalent A/FM1/47 vaccine given in 1971 produced a moderately good antibody response to A/USSR/90/77 in persons who are now over 23 years old.

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TABLE 1

Distribution of acute phase antibody titers of 23 unvaccinated influenza patients in HI tests with 5 influenza H3N2 strains

Test Strain	No. of persons with HI antibody titer of								
	<8	8	16	32	64	128	256	512	1024
A/HK/68	-	1	4	5	4	3	5	1	-
A/Eng/72	5	6	2	3	2	1	1	2	1
A/P.C./73	10	3	2	2	2	1	2	-	1
A/Vic/75	16	3	2	1	-	-	1	-	-
A/Den/77	20	2	-	-	1	-	-	-	-

TABLE 2

Distribution of acute phase antibody titers of 30 vaccinated influenza patients in tests with 5 influenza A H3N2 strains

Test Strain	No. of persons with HI antibody titer of								
	<8	8	16	32	64	128	256	512	1024
A/HK/68	2	1	1	3	2	5	2	5	9
A/Eng/72	4	1	1	5	2	2	7	3	6
A/P.C./73	4	1	4	2	3	3	2	7	5
A/Vic/75	15	2	3	3	4	2	1	-	-
A/Den/77	14	4	3	5	3	-	-	-	1

TABLE 3

Distribution of acute and convalescent complement fixing antibody titers of 23 unvaccinated and 30 vaccinated persons with influenza

		No. with C.F. antibody titer of									
		<8	8	16	32	64	128	256	512	1024	≥ 4 rise
Not Vaccinated	Acute	20	2	1	-	-	-	-	-	-	
	Conv.	-	-	2	7	5	7	2	-	-	96
Vaccinated	Acute	21	3	5	-	1	-	-	-	-	
	Conv.	1	1	1	9	6	9	3	-	-	87

TABLE 4

Distribution of acute and convalescent neuraminidase inhibiting antibody titers of 23 unvaccinated and 30 vaccinated persons with influenza

		No. with N.I. antibody titer of							% with ≥4 rise
		<4	4	8	16	32	64	≥128	
Not Vaccinated	Acute	17	-	3	3	-	-	-	87
	Conv.	2	-	2	7	4	3	5	
Vaccinated	Acute	4	7	7	7	3	-	2	67
	Conv.	2	1	2	4	5	8	8	

TABLE 5

Comparison of oral temperatures of vaccinated persons with NI antibody titers of 8 or less with those of persons with titers of 16 or more

Oral Temperature	NI antibody titer			
	8 or less		16 or more	
	No. of Persons	%	No. of Persons	%
99^8 or less	6	33	3	23
$100\text{-}100^8$	6	33	4	31
$101\text{-}101^8$	5	28	2	16
$\geq$ 102	1	6	4	31

TABLE 6

Comparison of fold increases in antibody titer in complement fixation, hemagglutination inhibitor (5 H3N2 strains) and neuraminidase inhibition tests with serum pairs from 23 unvaccinated patients with influenza

Test Used	Strain	No. of persons with fold increase in titer of								% with 4 fold rise
		0	2	4	8	16	32	64	128	
C.F.	A/Vic/75	-	1	2	7	4	9	-	-	96
H.I.	A/HK/68	6	6	8	1	-	2	-	-	48
	A/Eng/72	7	2	4	5	2	1	1	1	61
	A/P.C./73	6	2	2	6	5	-	-	2	65
	A/Vic/75	3	-	6	6	1	5	1	1	87
	A/Den/77	1	-	4	7	5	5	1	-	96
N.I.	X-48	2	1	5	7	3	2	3	-	87

TABLE 7

Distribution of HI antibody titers of 23 unvaccinated persons with influenza in tests with 5 influenza A H3N2 strains

Test Strain	Serum	No. with HI antibody titer of								
		8	8	16	32	64	128	256	512	1024
A/HK/68	Acute	-	1	4	5	4	3	5	1	-
	Conv.	-	-	1	1	5	6	3	3	4
A/Eng/72	Acute	5	6	2	3	2	1	1	2	1
	Conv.	1	1	1	4	3	5	1	5	2
A/P.C./73	Acute	10	3	2	2	2	1	2	-	1
	Conv.	2	-	1	3	8	1	2	3	3
A/Vic/75	Aucte	16	3	2	1	-	-	1	-	-
	Conv.	2	-	3	7	1	6	2	2	-
A/Den/77	Acute	20	2	-	-	1	-	-	-	-
	Conv.	1	-	3	6	6	3	3	1	-

TABLE 8

Comparison of fold increases in antibody titer in complement-fixation, hemagglutination inhibition (5 H3N2 strains) and neuraminidase inhibition tests with serum pairs from 30 previously vaccinated patients with influenza

Test	Virus Strain	No. with fold increase in antibody of									% with ≥4x rise
		0	2	4	8	16	32	64	128	256	
C.F.	A/Vic/75	2	2	5	8	6	6	2	-	-	87
H.I.	A/HK/68	17	9	1	3	1	-	-	-	-	17
	A/Eng/72	17	7	1	2	1	1	2	1	1	30
	A/P.C./73	13	6	4	2	2	1	1	1	1	40
	A/Vic/75	5	5	6	2	5	3	2	1	2	70
	A/Den/77	1	2	7	6	5	5	1	3	1	93
N.I.	X-48	7	3	11	4	4	2	-	-	-	65

TABLE 9

Distribution of HI antibody titers for 5 influenza A H3N2 strains of 30 vaccinated persons who became ill with influenza

Test Strain	Serum	No. of persons with HI antibody titer of								
		<8	8	16	32	64	128	256	512	1024
A/HK/68	Acute	2	1	1	3	2	5	2	5	8
	Conv.	1	-	-	1	5	3	3	6	11
A/Eng/72	Acute	4	1	1	5	2	2	7	3	5
	Conv.	1	-	1	1	4	5	6	6	6
A/P.C./73	Acute	4	1	4	2	3	3	2	7	4
	Conv.	-	1	2	1	3	6	6	3	9
A/Vic/75	Acute	15	2	3	3	4	2	-	-	-
	Conv.	1	1	4	1	6	6	6	2	3
A/Den/77	Acute	14	4	3	5	3	-	-	-	1
	Conv.	-	-	2	3	5	8	5	1	6

TABLE 10

COMPARISON OF KILBOURNE TEST (8-3-77) AND DENVER TEST (7-19-77)

		PR8 Antigen		Marine Antigen*	
Subject	Age	Kilbourne	Denver	Kilbourne	Denver
1	19	<10/<10	<8/<8	<10/<10	<8/128
2	18	<10/40	<8/256	<10/10	<8/256
3	19	<10/<10	<8/<8	<10/<10	<8/128
4	23	<10/80	8/1024	<10/40	8/1024
5	18	<10/<10	<8/<8	<10/<10	<8/256
8	24	<10/20	16/128	<10/10	64/256
9	24	<10/20	16/128	<10/10	64/512
10	23	<10/80	16/1024	<10/20	16/1024
13	18	<10/20	16/256	<10/40	16/512
15	38	<10/20	16/128	<10/10	64/1024
19	35	10/40	32/1024	<10/20	32/1024

*In Kilbourne test Marine antigen used at dilution of 1:14; in Denver test at dilution of 1:160

TABLE 11

Distribution of HI antibody titers of 50 persons following vaccination in tests with A/Victoria/75, A/Texas/77 and B/Hong Kong/72. Vaccine contained 400 CCA units of A/Victoria/75 (W.V.), 400 CCA units of A/New Jersey/76 (W.V.) and 500 CCA units of B/Hong Kong/72 (S.V.)

Test Strain	Percent of persons with HI titer of								
	<8	8	16	32	64	128	256	512	1024
A/Vic/75	-	4	14	24	22	20	6	6	4
A/Texas/77	4	10	18	16	12	20	6	12	2
B/HK/72	2	6	4	8	22	20	20	10	8

TABLE 12

A/FM1/47 HI antibody response following A/New Jersey/76 vaccine

Age Group	Serum Specimen	No. of persons with titer of									% with ≥4 rise	% ≥16
		<8	8	16	32	64	128	256	512	1024		
17-20*	Pre-	24	1	-	-	-	-	-	-	-		
	Post 1	17	4	1	1	1	1	-	-	-	16	16
	Post 2	6	3	6	8	1	1	-	-	-	60	64
23-32**	Pre-	11	5	8	8	3	3	-	-	-		
	Post-	4	1	2	7	6	6	7	3	2	63	87
Over 33**	Pre-	5	1	5	3	-	1	-	-	-		
	Post-	4	1	1	4	2	1	1	1	-	20	67

*First injection variable; second injection 400 CCA units of A/New Jersey/76 and of A/Victoria/74 M.S.D. vaccine.

**200 CCA units of A/New Jersey/76 and of A/Victoria/75

TABLE 13

A/AA/57 HI antibody response following A/New Jersey/76 vaccine

Age Group	Serum Specimen	No. of persons with titer of									% with ≥4 rise	% ≥16
		<8	8	16	32	64	128	256	512	1024		
17-20*	Pre-	23	2	-	-	-	-	-	-	-		
	Post 1	20	1	1	3	-	-	-	-	-	8	16
	Post 2	16	3	4	2	-	-	-	-	-	20	24
23-32**	Pre-	21	8	5	2	1	-	-	-	-		
	Post-	4	5	6	7	3	5	5	3	-	58	76
Over 33**	Pre-	7	4	4	-	-	-	-	-	-		
	Post-	7	3	3	2	-	-	-	-	-	0	33

*First injection variable; second injection 400 CCA units of A/New Jersey/76 and of A/Victoria/75 M.S.D. vaccine.

**200 CCA units of A/New Jersey/76 and of A/Victoria/75.

TABLE 14

A/USSR/90/77 HI antibody response following A/New Jersey/76 vaccine

Age Group	Serum Specimen	No. of persons with titer of									% with ≥4 rise	% ≥16
		<8	8	16	32	64	128	256	512	1024		
17-20	Pre-	25	-	-	-	-	-	-	-	-	4	4
	Post 1	23	1	1	-	-	-	-	-	-	0	0
	Post 2	24	2	-	-	-	-	-	-	-		
23-32	Pre-	16	5	10	4	3	-	-	-	-	55	74
	Post-	8	2	3	5	6	7	3	1	3		
Over 33	Pre-	10	3	1	-	-	-	1	-	-	13	33
	Post-	9	1	1	1	2	-	1	-	-		

TABLE 15

HI antibody titers for A/USSR/90/77 of 50 patients with febrile upper respiratory infections seen at Lowry Clinic between 11/1/77 and 12/9/77

Age	No. with HI titer of									%
	<8	8	16	32	64	128	256	512	1024	≥16
22 or less (36)	36	-	-	-	-	-	-	-	-	0
23 or more* (14)	7	-	1	-	2	1	3	-	-	50

*All were permanent party who had received A/New Jersey/76 vaccine a year before.

TABLE 16

A/FM1/47 HI antibody response following A/FM1/47 vaccine*

Age Group	Serum Specimen	No. of persons with titer of									% with ≥4 rise	% with titer ≥16
		<8	8	16	32	64	128	256	512	1024		
<17 (n=31)	Pre-	27	3	1	-	-	-	-	-	-		
	Post-	-	-	2	4	10	6	6	2	1	100	100
>18 (n=38)	Pre-	9	2	11	6	9	1	-	-	-		
	Post-	-	-	-	3	6	11	11	3	4	74	100

*Whole virus vaccine (Merrell-National) containing 571 CCA U/ml.

TABLE 17

A/USSR/90/77 HI antibody response following A/FM1/47 vaccine*

Age Group	Serum Specimen	No. of persons with titer of									% with ≥4 rise	% with titer ≥16
		<8	8	16	32	64	128	256	512	1024		
<17 (n=31)	Pre-	30	1	-	-	-	-	-	-	-		
	Post	15	4	5	5	2	-	-	-	-	39%	39%
>18 (n=38)	Pre-	19	4	5	8	2	-	-	-	-		
	Post-	6	-	3	15	8	6	-	-	-	47%	84%

*Whole virus vaccine (Merrell-National) containing 571 CCA U/ml.

TABLE 18

Comparison of oral temperatures of 23 unvaccinated persons with those of 31 vaccinated persons with influenza

Oral Temperature	Unvaccinated		Vaccinated	
	No. of Persons	%	No. of Persons	%
99^8 or less	3	13	9	29
$100\text{-}100^8$	7	30	10	32
$101\text{-}101^8$	4	17	7	23
Over 102	9	39	5	16

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

1) Antibody studies on 23 unvaccinated and 30 vaccinated persons with A/Texas/77 influenza showed that almost all had been infected previously with H3N2 strains. HI titers were highest against the earliest strain and diminished progressively with more recent strains. They were lowest with A/Denver/77, the epidemic strain. 2) Neuraminidase inhibiting (NI) antibody titers were low in the acute sera of unvaccinated persons, but 15 of 33 vaccinated persons had titers of ≥16. The NI titer levels were of less value in predicting protection against influenzal illness that HI antibody levels against the epidemic strain. --continued--

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(CONT.

3) The most useful tests for serodiagnosis were HI tests using the epidemic strain and complement-fixation tests. NI tests and HI tests with earlier H3N2 strains were less sensitive, particularly in vaccinated persons.
4) The Lowry Air Force Base population, which had received A/Victoria/75 vaccine in November, 1977 had only a scattering of cases of influenza even though influenza A, mainly A/Victoria/75, was widespread in the Denver area in December, 1977 and January, 1978.
5) HI tests for antibody for H1N1 strains showed that persons under 23 years of age lacked antibody for A/FM1/47, A/AA/57 or the new epidemic strain A/USSR/90/77. A large proportion of persons between 23 and 32 and a smaller proportion of older persons had antibody. Titers were considerably higher for A/FM1/47 than for A/AA/57 or A/USSR/90/77.
6) Persons between 23 and 32 who had received A/New Jersey/76 vaccine showed increases in titer to all 3 H1N1 strains. Persons younger or older than this showed almost no response in tests with A/USSR/90/77.
7) A monovalent A/FM1/47 vaccine given in 1971 produced a moderately good antibody response to A/USSR/90/77 in persons who are now over 23 years old.

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